# IMPROVING EXPOSURE ASSESSMENT BY MONITORING HUMAN TISSUES FOR TOXIC CHEMICALS

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*Typically, the availability of appropriate data to estimate human exposures to toxic chemicals is scarce. Consequently, exposure assessments are often based on indirect surrogates of exposure, such as a combination of questionnaire data on time-activities and concentrations of toxic chemicals measured in environmental media (e.g., air, water, food, soil, dust). Recent advances, however, make it technically feasible and relatively affordable to measure low levels of multiple toxic chemicals in accessible human tissues (e.g., blood, urine). The increasing availability of biological markers for exposure, along with improvements in pharmacokinetic understanding, present new opportunities to estimate exposure from human tissue measurements and from knowledge of intake and uptake parameters. Biological monitoring provides exposure information that is usually complementary to the type of exposure information obtained from environmental monitoring. Biological and environmental monitoring can be used separately or together in order to meet desired objectives. We present here a discussion of the value of biological monitoring for improving exposure assessment. We emphasize the role of biological monitoring in identifying high-priority exposures, evaluating the effectiveness of intervention and prevention efforts, identifying at-risk subpopulations, recognizing time trends in population exposures, establishing reference ranges of tissue concentrations, and providing integrated dose measurements.*

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**Journal of Exposure Analysis and Environmental Epidemiology, Vol. 5, No. 3, pp. 405–424**
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**ISSN: 1053-4245**

## INTRODUCTION

Informed decisions about protecting and promoting public health require adequate and appropriate information about exposures to environmental agents, as well as about related toxicity (NRC, 1991a,b,c,d; Sexton et al., 1995a; Wagener et al., 1995). But realistic exposure assessment is typically limited by a scarcity of information on actual exposures and related doses, and by a lack of knowledge about important exposure-related mechanisms, such as transport and fate processes, and pharmacokinetics. This paper explores how exposure assessments can benefit from measurements of toxic chemicals in human tissues and discusses why human tissue monitoring is an integral component of a national exposure surveillance program.

The discussion is organized into two major sections: 1) a description of exposure and dose in the context of exposure assessment; and 2) a survey of the value of human tissue monitoring in improving exposure assessment, especially as it relates to a national assessment of human exposure.

## EXPOSURE AND DOSE IN THE CONTEXT OF EXPOSURE ASSESSMENT

### *Defining Exposure and Dose*

For the purposes of this paper, and consistent with previous definitions and usages (NRC, 1991a,b,c,d; EPA, 1992), exposure is defined as contact of a biological, chemical, or physical agent with the outer surface of the human body, such as the skin, mouth, or nostrils. As shown in Figure 1, exposure is part of a series of events that has been referred to as an environmental health paradigm (Sexton et al., 1993a; 1995a). This simplified representation of the key steps from release of toxic agents into the environment to subsequent disease or dysfunction in people is useful to aid in understanding and evaluating environmental health risks.

In addition to exposure, several events in the paradigm have been defined in the Environmental Protection Agency's (EPA's) exposure assessment guidelines (EPA, 1992; Sexton et al., 1995a). Potential or administered dose is the amount of the agent that is actually ingested, inhaled, or applied to the skin; whereas applied dose is the amount of the agent directly in contact with the body's absorption barriers (e.g., skin, respiratory tract, gastrointestinal tract), and, therefore, available for absorption. The amount of the agent that enters the body is described as the internal or absorbed dose. That portion of the internal (absorbed) dose that reaches a tissue of interest is called delivered dose or body burden. The biologically effective (target) dose refers to that portion of the delivered dose (body burden) that reaches the site(s) of toxic action.

The link, if any, between biologically effective (target) dose and subsequent illness or injury depends on the relationship between dose and response (e.g., the shape of the dose-response curve), underlying pharmacodynamic mechanisms (e.g., compensation, damage, repair), and important susceptibility factors (e.g., health status, nutrition, genetic predisposition).

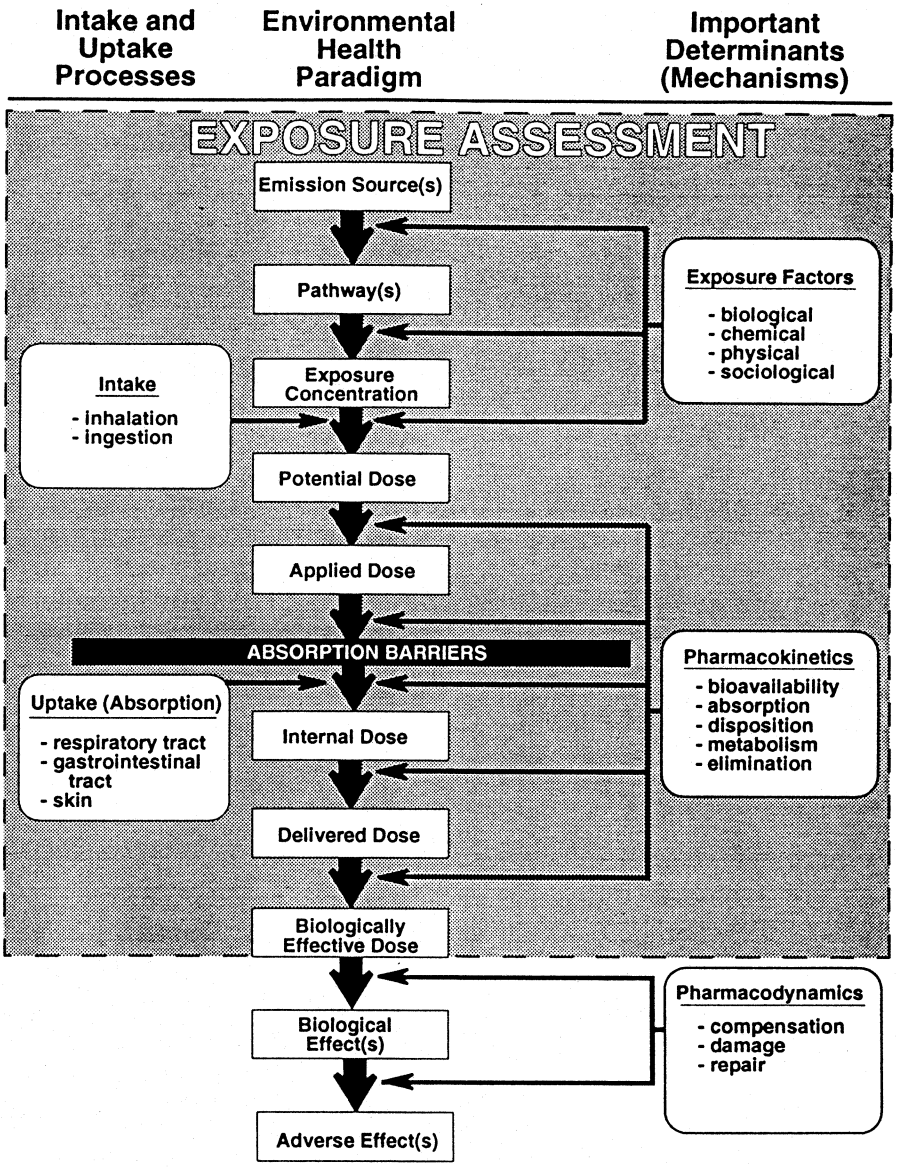


**FIGURE 1.** The domain of exposure assessment in relation to an environmental health paradigm (Sexton et al., 1995a).

*Linking Exposure and Dose*

A conceptual framework for visualizing the link between significant exposure- and dose-related events in the environmental health paradigm is illustrated in Figure 2 (Sexton et al., 1995a). The example assumes that complete information is available about a hypothetical population, which is exposed to a single chemical toxicant by multiple pathways and routes. In order to make realistic estimates about a specific event (e.g., internal dose), it is necessary

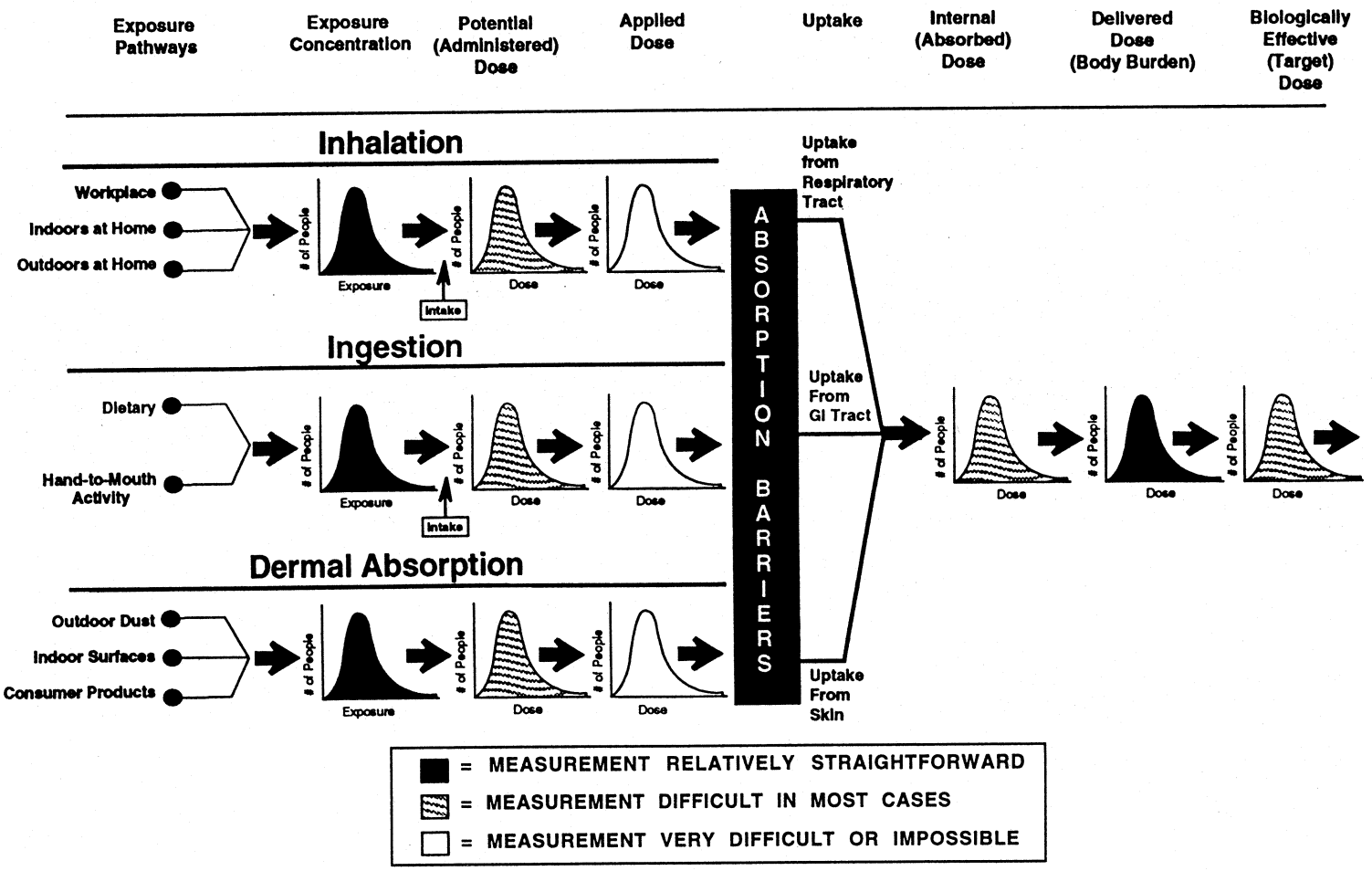


**FIGURE 2.** The relationship between important exposure-related and dose-related events in the context of exposure assessment (Sexton et al, 1995a).

to have at least one of two types of information: (1) direct measurements of the event itself; or (2) measurement of an earlier (e.g., potential dose) or a later (delivered dose) event, plus an understanding of the intervening mechanisms (e.g., pharmacokinetics) that govern the relationship between the measured event and the event of interest. Without such information, extrapolating from one event to another, moving from either exposure to dose (from left to right in Figure 2) or from dose to exposure (from right to left in Figure 2) is problematic.

In reality, suitable data and adequate understanding are seldom, if ever, on hand to describe and estimate all of the significant events with regard to the agents, situations, and populations of interest. The range of data collection methods and a comparison of their relative costs and abilities to classify/estimate exposures are summarized in Figure 3 (NRC, 1991a,b,c,d; EPA, 1992; Sexton et al., 1993b, 1995a).

*Exposure Assessment*

Risk-related exposure assessment involves the qualitative description and the quantitative estimation of an agent's contact with and entry into the body. Although no two exposure assessments are exactly the same, most address three areas that are important for risk assessment and risk management decisions: (1) the number of people exposed at specific concentrations for the time period of interest; (2) the resulting dose (e.g., internal, delivered,

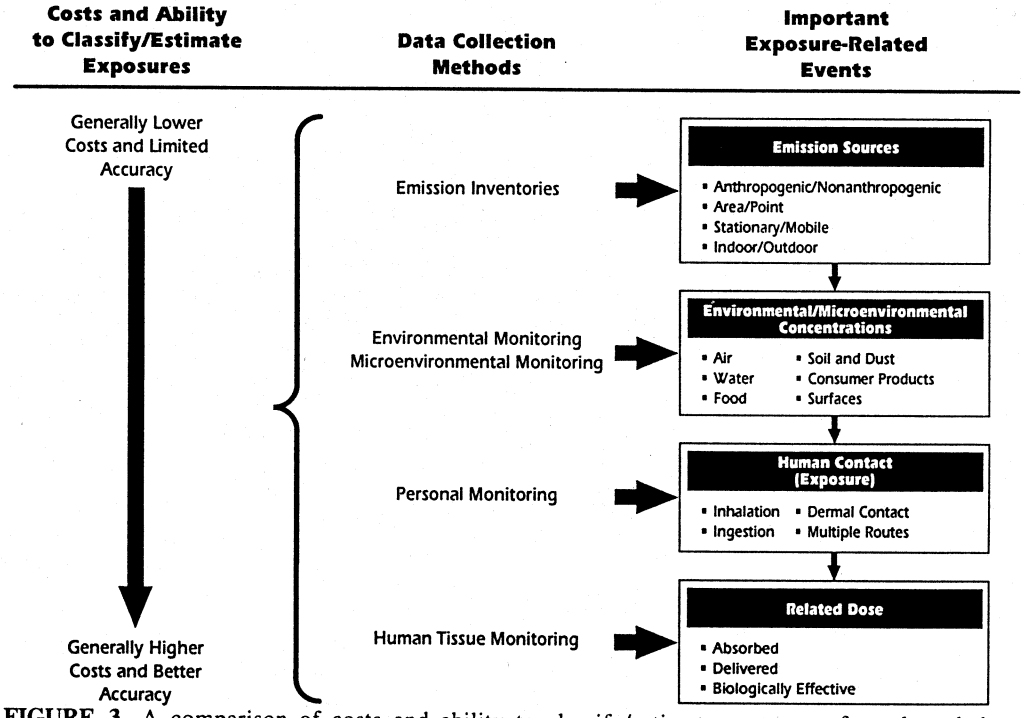


**FIGURE 3.** A comparison of costs and ability to classify/estimate exposures for selected data collection methods (Sexton et al., 1993b).

target); and (3) the contributions of important sources and pathways to exposure and dose. Thus, the domain of exposure assessment is quite extensive (Figure 1), encompassing many important events in the environmental health paradigm and entailing consideration of intake and uptake factors, important exposure factors, and pharmacokinetic mechanisms and processes (EPA, 1992; Sexton et al., 1995a).

The quantitative estimation of exposure, which is often a primary objective, can be approached in three general ways: (1) point-of-contact measurements — measurement of actual exposure as it occurs at the point of contact with the human body; (2) exposure reconstruction — estimation of exposure from measurement of dose based on a) reconstruction of internal dose from human tissue measurements and knowledge of relevant pharmacokinetics, and b) data or assumptions about intake and uptake rates; and (3) exposure scenarios — estimation of exposure using a hypothetical but plausible set of assumptions about important exposure-related factors (e.g., consumption rates) (EPA, 1992).

Because the necessary data were unavailable, it has usually been impractical or impossible in the past to use either point-of-contact measurements or reconstructive methods for exposure assessment. In constructing a plausible scenario that describes quantitatively how contact occurs between people and environmental agents, exposure assessors have, therefore, typically had to rely on the few available facts, in combination with assumptions, inferences, and professional judgment.

An exposure scenario is constructed using a logical, stepwise analysis of important events in the environmental health paradigm; from source(s), through pathways, to exposure, and ultimately to biologically effective dose. Important parameters, such as emission rates, product-use patterns, transport and fate processes, concentrations in food and water, human consumption patterns, uptake rates, metabolism, and excretion are either estimated from available data or assumed to be represented adequately by default values (EPA, 1992; Sexton et al., 1995a). The primary disadvantage of the scenario approach is that, because of a scarcity of data, it requires assumptions and inferences, which introduce substantial scientific uncertainty into the final exposure estimate (EPA, 1992; Sexton et al., 1995a).

*The Value of Human Tissue Monitoring in Improving Exposure Assessment*

Recent advances in the measurement of biological markers in accessible human tissues have made it technically feasible and relatively affordable to use biological monitoring to estimate exposures for more and more toxicants (Hulka et al., 1990; Sexton et al., 1995a). Many of the dose- and health-related events in the environmental health paradigm occur at inaccessible sites in the body (e.g., liver, developing organs). Biological markers (biomarkers) are indicators of these significant but inaccessible events that can be measured in accessible human tissues (e.g., blood, urine, saliva, exhaled breath). Over time, the state of the science in human tissue monitoring for toxic chemicals has improved dramatically, so that we now have: (1) more sensitive methods for priority toxicants; (2) the ability to make multiple

measurements per sample; (3) more sensitive, specific, and accurate measurement techniques, with better quality assurance and control; (4) reference ranges in human populations for many biological markers; and (5) better pharmacokinetic understanding.

The National Center for Environmental Health (NCEH), Centers for Disease Control and Prevention (CDC), has developed and refined methods for measuring biological markers in human tissues. The capabilities of the NCEH to measure low levels of multiple toxic chemicals (or their metabolites) in relatively small amounts of blood, serum, or urine are summarized in Table 1. It is evident that current technology enables the measurement of multiple analytes (i.e., metals, dioxins, furans, polychlorinated biphenyls, volatile organic compounds, pesticides), at relatively low limits of detection (i.e., low parts-per-billion and parts-per-trillion), in relatively small amounts of blood, serum, and/or urine (usually 10 ml or less). The NCEH and others continue to demonstrate the practicality and utility of measuring biological markers of exposure for many important environmental chemicals, and more and better biological measurements will become available in the future (NRC, 1989a,b, 1991a, 1992; Hulka et al., 1990; NCHS, 1994; Pirkle et al., 1994, 1995; Needham et al., 1995).

Because they have already contributed substantially to public health decisions about environmental health, several capabilities of biological monitoring merit special emphasis. Biological monitoring helps health officials:

- identify priority exposures
- evaluate the effectiveness of interventions and prevention efforts
- identify at-risk subpopulations
- recognize time trends in population exposures
- establish reference ranges of tissue concentrations
- obtain integrated (over all routes of exposure) dose measurements

*Identifying Priority Exposures*

People are exposed to thousands of chemicals in their everyday activities. Substances which have a greater potential for toxicity and that also tend to accumulate in the body are of the highest health concern. Biological monitoring provides direct information on which toxicants have managed to get into the body from environmental exposures and how much of the toxicant(s) has accumulated. Although dose-response relationships for health effects are not well-defined for most toxicants, a general principle of toxicology is that higher doses of toxicants increase the likelihood of adverse effects. Thus, blood or urine levels of toxicants that are much higher than those seen in the background population warrant additional attention. For toxicants that have better defined dose-response information (e.g., lead), biological monitoring is extremely valuable for determining a population's health risk from exposure.

For a given population, measurements in blood and urine of a profile of toxicants, which might include heavy metals, persistent and nonpersistent pesticides, volatile organic

**TABLE 1. Human Tissue Measurements Currently Performed at the National Center for Environmental Health (NCEH) of the Centers for Disease Control and Prevention (CDC)**

Metals (typical urine or blood sample — 3 ml; typical limit of detection — low parts-per-billion)

| | | |
|---|---|---|
| Lead | Arsenic | Chromium |
| Mercury | Vanadium | Nickel |
| Cadmium | Beryllium | Thallium |

Polychlorinated dibenzo-dioxins, polychlorinated dibenzo-furans, coplanar polychlorinated biphenyls (PCBs) (all analytes measured in serum from one 25-ml blood sample if exposure is near background levels — smaller samples are adequate for higher exposures; typical limit of detection — low parts-per-trillion on a lipid-weight basis, low parts-per-quadrillion on a whole weight basis)

| | |
|---|---|
| 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) | 2,3,4,7,8-Pentachlorodibenzofuran (PnCDF) |
| 1,2,3,7,8-Pentachlorodibenzo-p-dioxin (PnCDD) | 1,2,3,4,7,8-Hexachlorodibenzofuran (HxCDF) |
| 1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin (HxCDD) | 1,2,3,6,7,8-Hexachlorodibenzofuran (HxCDF) |
| 1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin (HxCDD) | 1,2,3,7,8,9-Hexachlorodibenzofuran (HxCDF) |
| 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (HxCDD) | 2,3,4,6,7,8-Hexachlorodibenzofuran (HxCDF) |
| 1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin (HpCDD) | 1,2,3,4,6,7,8-Heptachlorodibenzofuran (HpCDF) |
| 1,2,3,4,6,7,9-Heptachlorodibenzo-p-dioxin (HpCDD) | 1,2,3,4,7,8,9-Heptachlorodibenzofuran (HpCDF) |
| 1,2,3,4,6,7,8,9-Octachlorodibenzo-p-dioxin (OCDD) | 1,2,3,4,6,7,8,9-Octachlorodibenzofuran (OCDF) |
| 2,3,7,8-Tetrachlorodibenzofuran (TCDF) | 3,3',4,4'-Tetrachlorobiphenyl (TCB) |
| 1,2,3,7,8-Pentachlorodibenzofuran (PnCDF) | 3,4,4',5-Tetrachlorobiphenyl (TCB) |
| | 3,3',4,4',5-Pentachlorobiphenyl (PnCB) |
| | 3,3',4,4',5,5'-Hexachlorobiphenyl (HxCB) |

Volatile organic compounds (VOCs) (all analytes measured in one 10-ml blood sample; typical limit of detection — low parts-per-trillion)

| | | |
|---|---|---|
| 1,1,1-Trichloroethane | Acetone | Hexachloroethane |
| 1,1,2,2-Tetrachloroethane | Benzene | m-/p- Xylene |
| 1,1,2-Trichloroethane | Bromodichloromethane | Methylene chloride |
| 1,1-Dichloroethane | Bromoform | o-Xylene |
| 1,1-Dichloroethene | Carbon Tetrachloride | Styrene |
| 1,2-Dichlorobenzene | Chlorobenzene | Tetrachloroethene |
| 1,2-Dichloroethane | Chloroform | Toluene |
| 1,2-Dichloropropane | cis-1,2-Dichloroethene | trans-1,2-Dichloroethene |
| 1,3-Dichlorobenzene | Dibromochloromethane | Trichloroethene |
| 1,4-Dichlorobenzene | Dibromomethane | |
| 2-Butanone | Ethylbenzene | |

Chlorinated pesticides and noncoplanar polychlorinated biphenyls (all analytes measured in serum from one 5-ml blood sample; typical limits of detection — low parts-per-billion)

| | |
|---|---|
| Aldrin | DDE |
| Chlordane, alpha | DDT |
| Chlordane, gamma | Dieldrin |
| beta-Hexachlorocyclohexane | Endrin |
| gamma-Hexachlorocyclohexane | Heptachlor |
| Biphenyls, Polychlorinated (total) | Heptachlor epoxide |
| Biphenyls, Polychlorinated (individual congeners) | Hexachlorobenzene |
| DDD | Mirex |
| Trans-nonachlor | Oxychlordane |

**TABLE 1. Human Tissue Measurements Currently Performed at the National Center for Environmental Health (NCEH) of the Centers for Disease Control and Prevention (CDC) (cont'd)**

Nonpersistent pesticides (all analytes measured in one 10-ml urine sample; typical limits of detection — low parts-per-billion)

| Urine metabolites | Parent pesticide(s) |
|---|---|
| 2-Isopropoxyphenol (IPP) | Propoxur |
| 2,5-Dichlorophenol (25DCP) | 1,4-Dichlorobenzene |
| 2,4-Dichlorophenol (24DCP) | 1,3-Dichlorobenzene, dichlofenthion, prothiofos, phosdiphen |
| Carbofuranphenol | Carbofuran, benfuracarb, carbosulfan, furathiocarb |
| 2,4,6-Trichlorophenol (246TCP) | 1,3,5-Trichlorobenzene, hexachlorobenzene, lindane |
| 3,5,6-Trichloro-2-pyridinol (TCPY) | Chlorpyrifos, chlorpyrifos-methyl |
| 4-Nitrophenol (NP) | Parathion, methyl parathion, nitrobenzene, EPN |
| 2,4,5-Trichlorophenol (245TCP) | 1,2,4-Trichlorobenzene, fenchlorphos, trichloronate |
| 1-Naphthol (1NAP) | Naphthalene, carbaryl |
| 2-Naphthol (2NAP) | Naphthalene |
| 2,4-Dichlorophenoxyacetic acid (24D) | 2,4-D |
| Pentachlorophenol (PCP) | Pentachlorophenol |

compounds (VOCs), dioxins, furans, polychlorinated biphenyls (PCBs), polyaromatic hydrocarbons (PAHs), and aromatic amines, provide a useful screen for toxicant exposures of highest health priority. If reference range data are available for these toxicants in blood and urine, the population levels can be directly compared to background exposure levels. Based on questionnaire data, a subgroup of the population with highest likelihood of exposure can often be identified. Measurements of toxicants in blood or urine for this subgroup usually provide a good estimate of the upper end of exposure and identify which exposures are likely to be of most concern.

Blood lead levels have been a classic example of how biological monitoring can assess whether lead exposure is of high health priority. As results of more and better epidemiologic studies of lead toxicity have mounted, the blood-lead-level cutoff for health concern has dropped from 60 to 40 to 30 to 25 to 10 micrograms per deciliter (μg/dl) (Pirkle et al., 1994). Blood lead levels have characterized human exposure in numerous studies and are the public health gauge of the risk of health effects for an individual or a population (Annest et al., 1983; Carter-Pokras et al., 1990; CDC, 1991).

*Evaluating the Effectiveness of Interventions and Preventions*

Regulatory interventions and public health actions to reduce human exposure to toxicants need to be evaluated to assure that they have been effective. Population-based biological monitoring over time allows direct comparison of how much body burden exists in a population before and after regulatory and public health interventions and preventions. This "before and after" evaluation is also useful to compare the relative costs and benefits of different interventions such as different approaches to reducing exposure to lead from lead-based paint.

As a result of the introduction of cars requiring unleaded gasoline into the U.S. fleet in about 1975, the amount of lead used in gasoline began to decline in the United States. From 1976 to 1980, the second National Health and Nutrition Examination Survey (NHANES II) measured blood lead levels in the U.S. population (Mahaffey et al., 1982; Annest et al., 1983), providing results of blood lead measurements of over 9,000 Americans. As lead in gasoline decreased about 55%, mean blood lead levels dropped correspondingly, decreasing a total of 6 μg/dl or about 37% (Mahaffey et al., 1982; Annest et al., 1983).

The amount of lead in gasoline continued to decline after 1980. From 1976 to 1990, the amount of lead used in gasoline decreased 99.8%, from 186.47 to 0.47 million kg (EPA, 1991). NHANES III - Phase 1 was conducted from October 1988 through October 1991 and included blood lead measurements. The continued decline in use of gasoline lead and the decrease in lead used in soldered cans resulted in an overall decline of 78% in mean blood lead levels from NHANES II to NHANES III - Phase 1 (Pirkle et al., 1994). Over the same period, the percentage of children of ages 1–5 years with blood lead levels of 10 μg/dl or higher decreased from 88.2% to 8.9%. Biological monitoring demonstrated the effectiveness of removing lead from gasoline and soldered cans; this measure was shown to reduce substantially the exposure of the U.S. population to lead. The change in the blood lead levels of the mean population and in the percentage of children with excessive blood lead levels are shown in Figures 4 and 5.

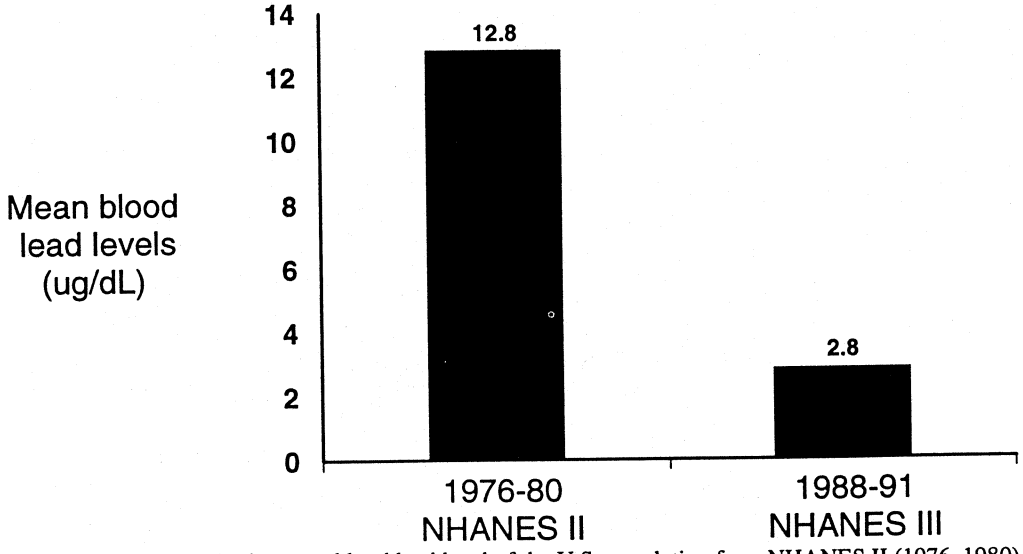


**FIGURE 4.** Change in the mean blood lead level of the U.S. population from NHANES II (1976–1980) to NHANES III (1988–1991) (data from Pirkle et al., 1994).

Similarly, in the 1970s, the National Human Adipose Tissue Survey (NHATS) was instrumental in documenting widespread prevalence of pesticide residues in residents of the U.S., and in identifying a high-risk subpopulation exposed to the pesticide Mirex. The

NHATS showed that reductions in the use of PCBs, DDT, and dieldrin were followed by a decline in adipose tissue concentrations, and it revealed a dramatic decline in PCB tissue concentrations after the 1976 regulation of PCBs (NRC, 1991a).

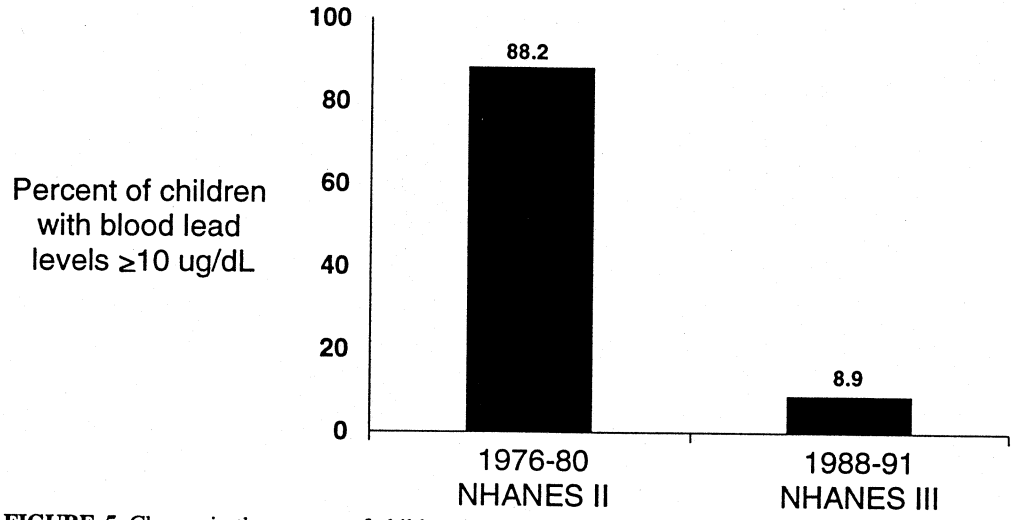


**FIGURE 5.** Change in the percent of children in the United States aged 1–5 years with elevated blood lead levels from NHANES II (1976–1980) to NHANES III (1988–1991) (data from Pirkle et al., 1994).

*Identifying At-Risk Subpopulations*

Exposure information about the general population does not, by itself, reveal differences in exposures between important population subgroups, such as those defined by sociodemographic characteristics or geographic location. Exposure differences can result, for example, from increased risk of exposure because of differences in personal habits (e.g., smoking), occupation (e.g., working with hazardous chemicals), proximity to emission sources (e.g., residence near freeway), cultural practices (e.g., eating fish as part of tribal heritage), or other factors.

For many toxicants, exposures tend to occur through multiple pathways and routes, and are subject to a variety of modifying factors that influence how much of a toxicant actually enters the body. Therefore, direct measurements of body burden based on biological monitoring can be a valuable tool in identifying the population subgroups who experience higher exposures. Careful study design in population-based exposure studies can assure adequate sampling of the subgroups of interest (Carter-Pokras et al., 1990).

Blood lead measurements have shown that in the United States certain sociodemographic groups are at a higher risk of excessive exposure, including African-Americans, Hispanics, low-income families, and those living in urban areas (Brody et al., 1994). Figure 6 shows the percentage of children in the United States aged 1–5 years who have elevated blood lead

levels, stratified by race/ethnicity and place of residence. Elevated blood lead levels are more common among African-Americans than among whites or Hispanics. Among African-American children, those living in central cities with populations greater than one million are at the highest risk of elevated blood lead levels (prevalence of 36.7%).

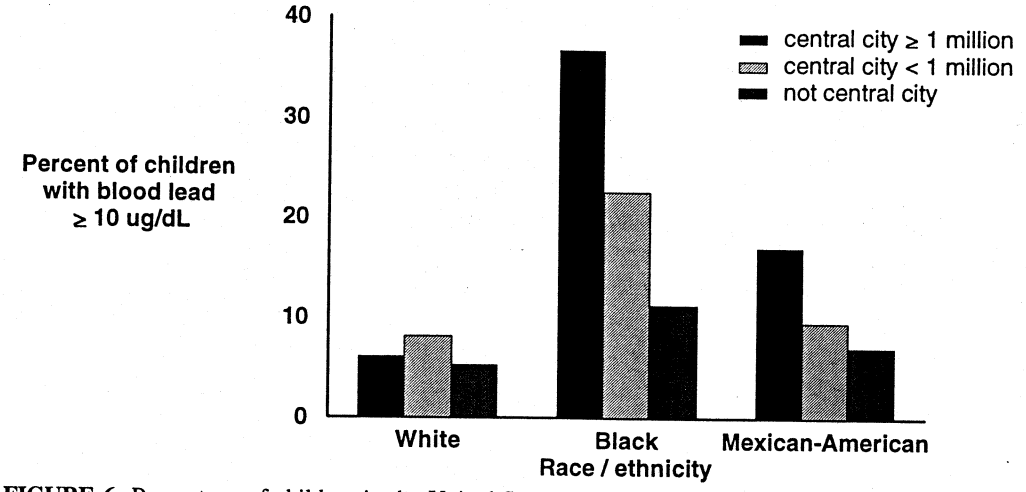


**FIGURE 6.** Percentage of children in the United States with elevated blood lead levels, stratified by race/ethnicity and place of residence. Estimate for white children in central cities with more than one million persons may be unstable due to small sample size (data from Brody et al., 1994).

Overall, younger children have higher blood lead levels than older children; the blood levels of older adults are higher than those of younger adults, and males have higher levels than females (Brody et al., 1994). These findings are particularly helpful in targeting intervention resources toward the population subgroups at greatest risk of excessive exposure.

PCBs provide another example. Since PCBs can bioaccumulate in the fatty tissue of certain fish, individuals who consume large amounts of these fish are potentially more highly exposed. Due largely to uncertainties in the determination of the types and quantities of fish actually eaten, considerable uncertainty can accompany modeling efforts aimed at estimating the amount of PCBs consumed. Scientists have successfully used biological monitoring to bypass this uncertainty by directly measuring the body burden of PCBs in fish eaters (Needham et al., 1992, 1995).

Exposure to environmental tobacco smoke (ETS) is also difficult to quantify using questionnaire data. Environmental monitoring data coupled with time-activity data are useful, if they are available. Biological monitoring of cotinine, a nicotine metabolite, provides an unbiased estimate of an individual's exposure to nicotine during the past few days (Jarvis et al., 1984, 1988; Watts et al., 1990). Cotinine measurements have been extremely useful in identifying population subgroups who are at higher risk of ETS exposure and in linking exposure to adverse health effects. Measurements of serum cotinine in NHANES III - Phase 1

(1988–1991) characterize the exposure of the U.S. population to both active and passive smoking, as well as the relative exposure of many population subgroups in the United States (NCHS, 1994).

*Recognizing Time Trends in Population Exposures*

People are exposed to literally millions of chemicals. Rational public health policy calls for a much clearer understanding of which chemicals are actually accumulating in the body over time. For example, does increased use of cadmium in nickel/cadmium batteries and other products result in an increased exposure in the population? If so, how much? Similarly, does the increased use of benzene in gasoline result in an accumulation of protein adducts of benzene in the body?

To determine which toxicants are accumulating in people in the United States, it is necessary to monitor over time the toxicant levels in blood, serum, and urine of a representative sample of the U.S. population. NHANES II was the first study to measure blood lead levels on a sample of persons who were representative of the U.S. population. NHANES II data showed that the decreasing amount of lead used in gasoline was paralleled by a decrease in blood lead levels. Had such studies been done earlier, i.e., when the amount of lead used in gasoline was increasing, public health officials would have known much sooner that gasoline lead was a major source of lead exposure.

As part of NHANES III, cadmium is being measured in urine (NCHS, 1994). These biological monitoring measurements are part of the first study of the U.S. population that will lead to a definition of cadmium exposure. Future NHANES studies, starting in 1998, will reexamine cadmium levels to determine whether an increased use of cadmium in the United States is resulting in an increased exposure in the general population or in population subgroups.

*Establishing Reference Ranges*

Human studies of exposure and health effects often lack appropriate comparison groups to interpret properly biological monitoring measurements. Reference ranges are biological measurements obtained in a reference population, which is typically a population with no known exposure or with only minimal exposure to the toxicant of concern.

Reference ranges are particularly useful when interpreting exposure measurements that are not collected as part of a population-based probability sample. For example, if a person is concerned about possible recent lead exposure and has her or his blood lead level tested, a measured blood lead level of 3 μg/dl would indicate exposure at about the 50th percentile of the U.S. population (Brody et al., 1994). This blood lead measurement would reassure the individual that no excessive exposure had occurred and that no special medical action was needed.

On the other hand, dioxin (2,3,7,8-TCDD) is present in the general population at serum levels (on a lipid basis) of less than 20 and usually less than 10 parts per trillion (ppt). If a person

had no clear memory of exposure to dioxin, but had a serum dioxin level of 5000 ppt, medical follow-up as well as follow-up to identify the source of exposure and to prevent additional exposure would be warranted.

In studies of exposures around hazardous waste sites, industrial emission sources, and other point sources, it is not always possible to have a control population of sufficient size to give an adequate reference or comparison range. In these cases, reference ranges established in other studies provide helpful information for interpretation.

As part of NHANES III, approximately 1,000 individuals provided blood and urine samples to determine reference ranges for 32 VOCs in blood and 12 pesticides in urine (NCHS, 1994). These individuals were selected to sample demographic subgroups defined by age, sex, race/ethnicity, urban/rural status, and region of the country. The VOCs analyzed included benzene, toluene, styrene, ethylbenzene, xylene, chlorobenzene, methylene chloride, 2-butanone, tetrachloroethylene, 1,1-dichloroethane, 1,2-dichloroethane, and others. Reference ranges for selected VOCs are given in Figure 7 (Ashley et al., 1994).

The urinary measurements included metabolites of pesticides such as carbaryl, naphthalene, propoxur, carbofuran, parathion, and chlorpyrifos. With the reference ranges found, it is now possible for scientists to determine whether levels of VOCs or pesticides measured in other studies are within "background" levels.

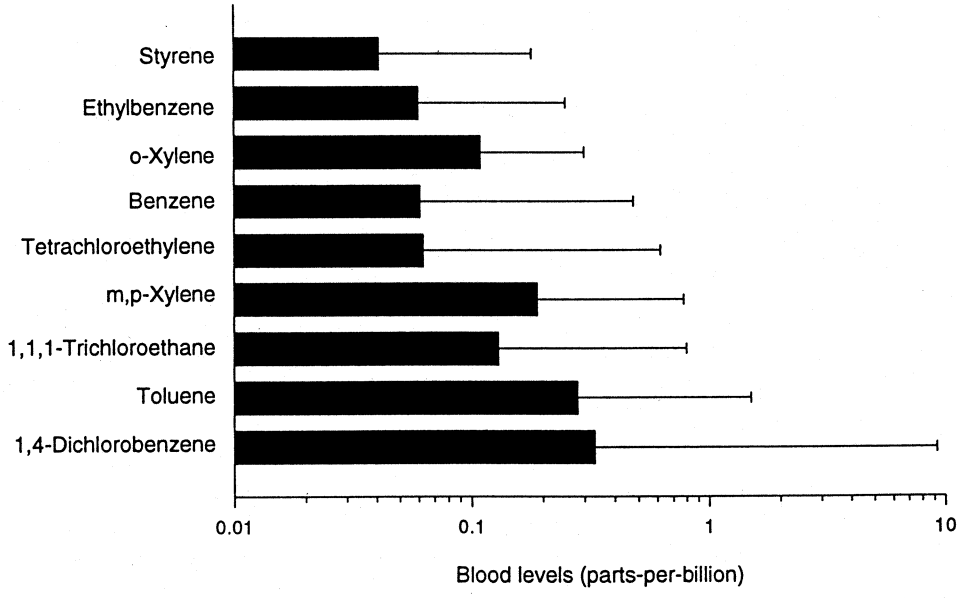


**FIGURE 7.** Reference ranges (50th and 95th percentiles) for blood levels (ppb) of selected volatile organic compounds in a reference population of persons with no known excessive exposures (n is greater than 500 for each VOC; data from Ashley et al., 1994).

*Providing Integrated Dose Measurements*

Exposure models generally estimate exposure concentrations by combining information about concentrations of the toxicant in relevant environmental media (e.g., air, food, water) with human time-activity patterns. Then, using assumptions about intake and uptake, the internal dose can be estimated, followed by an estimation of the delivered dose. Because biological measurements of delivered dose (body burden) are represented as an integrated concentration across all routes of exposure, they can be compared to these modeling predictions and their validity can thus be tested.

Scientists comparing biological monitoring measurements to predictions from exposure modeling need to consider the pharmacokinetics of the measured toxicant. For instance, dioxin (2,3,7,8-TCDD) has an estimated half-life greater than 7 years (Pirkle et al., 1989; Wolfe et al., 1994). Thus, measurement of a serum dioxin level would reflect exposure over many years. By contrast, whole blood benzene measurements represent exposure predominantly from the day preceding measurement, while benzene hemoglobin adducts integrate benzene exposure over the last four months.

A promising area of development for biological markers of exposure is the testing of hemoglobin adducts from red blood cells of different ages. By selecting fractions of red blood cells of different ages, it should be possible to provide a time-resolved measurement of hemoglobin adducts of toxicants for almost any two- or three-week period during the four months prior to the time of drawing the sample. NCEH is currently trying to develop such time-resolved measurements of hemoglobin adducts to assess exposure to VOCs, PAHs, selected pesticides, aromatic amines, and selected other toxicants. If successful, sequential, time-resolved measurements would allow a point-in-time (e.g., one-day or one-week) exposure to be distinguished from the typical exposure that the individual experiences. That is, the hemoglobin adduct measurements for "unexposed" time periods would provide the individual's background level, against which the levels for the "exposed" time periods could be compared directly to determine the magnitude of the point-in-time exposure.

If toxicants have biological markers that represent different integrating times (e.g., serum level and urine metabolite level), it is possible to select the marker most appropriate for the exposure time period of interest. For example, a short-term exposure (e.g., hours) could be compared to a human tissue concentration (e.g., whole blood) reflecting that same time period; medium-term exposures (e.g., days, weeks) could be compared to medium-term biomarkers (e.g., hemoglobin adducts); and longer-term exposures (e.g., years) to longer-term biomarkers (e.g., serum lipid or adipose tissue concentrations).

If exposure modeling predictions agree well with biological measurements, scientists have increased confidence that sources and pathways of exposure have been modeled appropriately. But, if biological monitoring measurements indicate that tissue concentrations are higher than predicted, the exposure model may need to be modified to include other

sources, pathways, or routes of exposure. In the early 1980s, data on blood lead levels helped scientists determine that lead in dust was a more important source of exposure than previously thought (EPA, 1986).

*High-Quality Analytical Measurements*

If biological monitoring is to reach its potential, high-quality analytical measurements are absolutely essential. Both environmental monitoring and biological monitoring use advanced analytical technologies (frequently hybrid technologies), including gas chromatography, liquid chromatography, and mass spectrometry. These analytical measurements need to be accurate, precise, sensitive, and specific. To assure comparability between studies and valid interpretation of individual measurements, biological monitoring measurements should be linked to the optimum accuracy base, such as reference materials from the National Institute of Standards and Technology (NIST). The accuracy base should be maintained over time, so that future measurements are directly comparable with previous studies.

The more precise the analytical measurements, the more power will be afforded the study or survey. Improving analytical precision to improve statistical power of a study or survey is sometimes better than increasing the number of participants. When interpreting analytical data, scientists should recognize that measurements close to the limit of detection of a particular method will be subject to greater analytical variability.

Biological monitoring measurements are often very demanding on analytical sensitivity. In practical terms, analytical sensitivity is an expression of how small a concentration can be validly distinguished from zero concentration. Usually, biological monitoring methods need to measure levels 10–1,000 times lower than similar environmental measurements. For example, analysis of water for a toxicant may start with one or two gallons of water. Biological monitoring typically starts with 3–50 ml of blood or urine, usually closer to 3 ml. The absolute mass of a toxicant entering the measurement system is therefore much lower, demanding more sensitive analytical methods.

On a whole weight basis, serum dioxin measurements must have a limit of detection in the low parts-per-quadrillion range (ppq) (Patterson et al., 1987). VOCs are often present in the blood in the low parts-per-trillion range (ppt) (Needham et al., 1995). Measurements at these low levels require excellent separation of the toxicant from interferents and other compounds as well as sensitive analytical methods employing such technologies as high resolution gas chromatography–high resolution mass spectrometry, and liquid chromatography tandem mass spectrometry.

*National Human Exposure Assessment Survey*

The NHEXAS is a federal interagency effort (e.g., EPA, CDC/NCEH, FDA, NIST) established to design and implement an ongoing system for surveillance of exposures to toxic chemicals in the U.S. population (Sexton et al., 1995b). The goal of NHEXAS is to document

the occurrence, distribution, and determinants of exposure of the U.S. population to hazardous environmental chemicals, including an analysis of geographic and temporal trends; to understand the determinants of exposure for potentially at-risk population subgroups, as a key element in the development of cost-effective strategies to prevent and reduce exposures deemed to be unacceptable; and to provide data and methods for linking information on exposures, doses, and health outcomes that will improve environmental health surveillance, enhance epidemiologic investigations, promote development of predictive models, and ultimately lead to better decisions about the assessment, management, and communication of health risks.

The NHEXAS will obtain a population-based, probability sample of U.S. residents and use a variety of methods to measure each participant's "total" exposure, through all important pathways and routes, to multiple toxic chemicals. Data collection methods will include questionnaires, diaries, environmental sampling, and human tissue monitoring.

The human-tissue-monitoring part of NHEXAS responds to the recommendation of the National Research Council (NRC, 1991a), which, in its 1991 report, called for a national monitoring effort aimed at providing estimates of exposure to toxic chemicals for the general population and for important population subgroups. The report said the NRC committee "... finds that a program of human tissue monitoring is critically necessary to continuing improvement of understanding exposure to toxic chemicals and recommends that such a program be given high priority for funds and other resources."

The NRC pointed out that environmental monitoring, as for example in air, water, food, or soil, is not by itself an adequate basis for assessing human exposures, and that human monitoring can serve, in effect, to integrate an understanding of many kinds of human exposures across media and time. They concluded that "A well-defined national program to monitor toxic chemicals in human tissues is a necessary component of an anticipatory strategy aimed at early identification of and response to health and environmental problems concerning xenobiotic toxicants in the environment" (NRC, 1991a).

The NRC supported tissue monitoring because: (1) tissue samples reflect exposures accumulated over time, (2) tissue samples reflect exposures by all routes, including some that are difficult or impossible to assess by environmental measurement (such as hand-to-mouth ingestion in young children), (3) pollutants in tissue samples have undergone the modifying effects of physiology (rates of uptake, distribution, bioconversion, elimination, and storage) and biological availability, (4) some agents are more concentrated, and so more readily detectable, in tissue samples than in the environment, and (5) tissue samples offer the opportunity to correlate, within a given person, the tissue concentration of toxicants with other tissue-based biological markers or indicators of effect that might predict injury or disease.

By including both tissue monitoring and environmental monitoring, the NHEXAS will provide an unusually complete assessment of exposure. If successful, this survey will provide the best available characterization of exposure of the U.S. population to priority toxicants.

## CONCLUSIONS

A scientifically credible assessment of exposures to environmental toxicants is a vital element of risk assessment and a key factor in making informed decisions about preventing or reducing risks deemed to be unacceptable. But a scarcity of data on actual exposures and doses in people has meant that most exposure assessments are necessarily based on constructions of hypothetical scenarios, which introduce significant scientific uncertainty into decision making. Biological monitoring provides valuable data on dose-related events and can improve the accuracy and strengthen the credibility of exposure assessments.

Human tissue monitoring for toxic chemicals is included in a major federal interagency effort to design and implement a system for exposure surveillance in the U.S. population. As part of the National Human Exposure Assessment Survey (NHEXAS), data from questionnaires, diaries, environmental monitoring, and biological monitoring will be used to determine baseline exposure for the general population and exposure for important population subgroups. The goal is to provide decision makers with data on historical trends and current status of exposures so that they can make more informed choices about protecting and promoting public health.

Recent advances in the measurement of toxic chemicals or their metabolites in accessible human tissues have made it technically feasible and relatively affordable to measure low levels (e.g., parts-per-billion to parts-per-quadrillion) of multiple toxic chemicals (e.g., heavy metals, VOCs, pesticides, PAHs, dioxins, PCBs, furans) in relatively small amounts (e.g., 3 ml to 50 ml) of blood, serum, or urine. These capabilities mean that we can use human tissue monitoring to help: (1) identify priority exposures, (2) evaluate the effectiveness of risk mitigation (e.g., exposure reduction/prevention) efforts, (3) identify at-risk subpopulations, (4) recognize trends in population exposures, (5) establish reference ranges of tissue concentrations, and (6) provide integrated (over all pathways/routes) dose measurements. Success in using biological measurements to improve exposure assessments requires active efforts to ensure high analytical quality is maintained. In the future, biological monitoring measurements should become available for more and more chemicals and methods will continue to get more accurate, precise, sensitive, and specific.

## DISCLAIMER

The views expressed are solely those of the authors and do not necessarily reflect the views or policies of their respective agencies.

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